PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Jose Rocca, et al.
Serial No.:	10/086,059
Filing Date:	27 February 2002
Title:	A SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION
Attorney Docket Number:	200541-7095

Attention Office of Petitions
Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir;

PETITION TO REVIVE FOR FAILURE TO TIMELY RESPOND TO OFFICE ACTION

Applicant hereby files this Petition to Revive and withdraw any holding of abandonment of the above-identified application for U.S. patent for failure to timely respond to Office Action.

The above-identified applications for U.S. patent became abandoned for failure to timely respond to an Office Action mailed on 16 April 2004. The abandonment date therefore is 16 October 2004.

Applicant respectfully submits that the abandonment of the above-identified application for U.S. patent was unintentional. The entire delay in filing the required reply i.e., filing a response or RCE, from the due date for the reply until the filing of this petition was unintentional. The delay was caused by a faulty docketing system which failed to provide warning to the upcoming due date.

Please charge our deposit account number 50-2543 the appropriate fee of $1500.00. Additionally, please credit any overpayment or charge any additional fees necessary revive this application to this deposit account.

04/21/2005 MBIZUNES 00000047 502543 10086059
01 FC:1453 1500.00 DA

Since this application was filed after 8th June 1995, no Terminal Disclaimer is required.

As 16th April 2005 fell on a Saturday, this submission is considered timely filed.

If there are any questions, please call the undersigned at the telephone number indicated below.

Respectfully submitted,

Kos Pharmaceuticals, Inc.

Karen J. Messick, Esq.
Attorney for Applicants
Reg. No. 46,256

Kos Pharmaceuticals, Inc.
2200 North Commerce Parkway
Suite 300
Weston, FL 33326
Tel.: (954) 331.3825
Fax: (954) 331.3867

Date: 4/18/05

CERTIFICATION UNDER 37 C.F.R., §1.10

I hereby certify that the attached papers are being deposited with the United States Postal service as: Express Mail Post Office to Addressee" Service under 37 C.F.R. §1.10 on April 18, 2005 and is addressed to Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

EL 955 246 419 US
Express Mail Label Number

Jared G. Silberhorn

04-20-05

DAE

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Jose Rocca, et al.
Serial No.:	10/086,059
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Attention Office of Petitions
Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir;

TRANSMITTAL LETTER

Enclosed for filing in the above-identified patent application are the following documents:

1. Petition to Revive Unintentionally Abandoned Patent Application;
2. Response to Office Action mailed on 16th April 2004;
3. Copy of Request for Continued Examination filed on 18th April 2005; and
4. Return Postcard.

As April 16th fell on a Saturday, this submission is considered timely filed.

If there are any questions, please call the undersigned at the telephone number indicated below.

Respectfully submitted,

Kos Pharmaceuticals, Inc.

Karen J. Messick, Esq.
Attorney for Applicants
Reg. No. 46,256

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Suite 300
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Tel.: (954) 331.3825
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EL 955 246 419 US
Express Mail Label Number

Jared Silberhorn

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Gutierrez-Rocca, et al.
Serial No.:	10/086,059
Filing Date:	02/27/2002
Docket Number:	540591-7095.1
Examiner:	Theodore J. Criares
Art Unit:	1617
Title:	A SUSTAINED RELEASED PHARMACEUTICAL FORMULATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Dear Sir:

In response to the Office Action mailed April 16, 2004 in connection with the above identified application for U.S. patent, please find the Application's response below:

Amendments to the Claims are reflected in the Listing of Claims, which begin on page 2 of this paper;

Remarks begin on page 9 of this paper.

Listing of Claims

Claims 1-5 and 7-16 are currently pending in the application.

Claim 1 (Currently amended) A sustained/prolonged release pharmaceutical formulation comprising:

(a) a water soluble medicament associated with; [and]

(b) a polymer mixture comprising a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent polyvinyl pyrrolidone of the total weight of said first component, combined with a second component comprising a cellulose ether polymer wherein said first component is present in an amount ranging from about 45 weight percent to about 90 weight percent of the total formulation.

Please cancel claim 2 without prejudice.

Claim 2 (Previously amended) A pharmaceutical unit dosage form which comprises:

(a) a water soluble medicament; and

(b) a polymer mixture comprising a first component present in an amount ranging from about 20 weight percent to about 90 weight percent of the total formulation combined with a second component comprising a cellulose ether polymer where said second component ranges from about 2 weight percent to about 60 weight percent of the total weight of the formulation.

Claim 3 (Twice amended) The [dosage form] formulation according to claim [2] 1 wherein said cellulose ether polymer is selected from the group consisting of methyl-, ethyl-, hydroxyethyl-, hydroxypropyl-, or hydroxypropyl methyl- substituted polymers of Methocel A series; hydroxypropyl methyl celluloses of METHOCEL E, F, J ,or K series at various viscosity grades; different viscosity grades of hydroxyl propyl celluloses of Klucel, or Methocel series; a low substituted grades of hydroxypropyl celluloses of the LH series; and ethyl celluloses of ETHOCEL P series, or a mixture of any of the foregoing ethers.

Claim 4 (Currently amended) The formulation according to claim [3] 1 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metoclopramide, a pharmaceutically acceptable acid addition salt of ranitidine, a pharmaceutically acceptable acid addition salt of captopril, a pharmaceutically acceptable acid addition salt of nefazodone, a pharmaceutically acceptable acid addition salt of zolpidem, a pharmaceutical acceptable acid addition salt of sertraline, a pharmaceutically acceptable acid addition salt of labetalol, and a pharmaceutically acceptable acid addition salt of atenolol.

(Remainder of page left intentionally blank)

Please cancel claim 5 without prejudice.

Claim 5 (Previously amended) A pharmaceutical construct comprising:

(a) a water soluble medicament;

(b) a polymer mixture comprising (a') a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent polyvinyl pyrrolidone of the total weight of said first component; combined with (b') a second component comprising a cellulose ether polymer ranging in an amount of from about 20 weight percent to about 60 weight percent of the total weight of the formulation.

Claim 6 (Previously cancelled) The pharmaceutical construct as defined in claim 5, wherein said first component is present in an amount ranging from about 20 weight percent to about 90 weight percent of the total formulation and said second component ranges from about 2 weight percent to about 60 weight percent of the total formulation.

Please cancel claim 7 without prejudice.

Claim 7 (Previously amended) The pharmaceutical construct as defined in claim 5 wherein said cellulose ether is selected from the group consisting of methyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methyl cellulose METHOCEL A series, METHOCEL E series, METHOCEL F series, METHOCEL K series, Metoloses LH series, ETHOCEL P series, or a mixture of any of the foregoing cellulose ethers.

Please cancel claim 8 without prejudice.

Claim 8 (Original) The pharmaceutical construct as defined in claim 7 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metoclopramide, a pharmaceutically acceptable acid addition salt of ranitidine, a pharmaceutically acceptable acid addition salt of captopril, a pharmaceutically acceptable acid addition salt of nefazodone, a pharmaceutically acceptable acid addition salt of zolpidem, a pharmaceutical acceptable acid addition salt of sertraline, a pharmaceutically acceptable acid addition salt of labetalol, and a pharmaceutically acceptable acid addition salt of atenolol.

Claim 9 (Currently amended) A process for the preparation of [a] <u>the</u> sustained/prolonged release pharmaceutical [unit dosage form] <u>formulation of claim 1</u> comprising the steps of:

(a) fluidizing a water soluble medicament combined with a carrier, comprising a polymer mixture comprising a fist component, comprising about 80 weight percent of polyvinyl acetate combined with bout 20 weight percent of polyvinyl pyrrolidone of the total weight of said first component, combined with a second component comprising a cellulose ether polymer; to from a fluidized mixture;

(b) direct blending the mixture to form a granulated mixture; and

(c) tabletting said granulated mixture and/or blend to form a tablet.

Claim 10 (Original) The process according to claim 9 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metoclopramide, a pharmaceutically acceptable acid addition salt of ranitidine, a pharmaceutically acceptable acid addition salt of captopril, a pharmaceutically acceptable acid addition salt of nefazodone, a pharmaceutically acceptable acid addition salt of zolpidem, a pharmaceutical acceptable acid addition salt of sertraline, a pharmaceutically acceptable acid addition salt of labetalol, and a pharmaceutically acceptable acid addition salt of atenolol.

Claim 11 (Twice amended) The [dosage form] formulation as defined in claim [2] 1 which comprises a modulated release pharmaceutical construct having a matrix of water soluble medicament associated with a polymer mixture, where said mixture comprises said first component combined with [a] said second component and said medicament associated with said matrix.

(Remainder of page left intentionally blank.)

Please cancel claim 12 without prejudice.

Claim 12 (Original) A sustained release pharmaceutical composition comprising a construct comprising a water soluble medicament and a polymer mixture, comprising a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of the total weight of said first component of polyvinyl pyrrolidone, combined with a second component comprising a cellulose ether polymer.

Claim 13 (Currently amended) A process for preparing [a] the sustained/prolonged release pharmaceutical formulation of claim 1 [unit dosage form], which comprises:

(a) blending a water soluble medicament with a polymer mixture comprising a first component, comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of polyvinyl pyrrolidone of the total weight of said first component, combined with a second component, comprising a cellulose ether polymer, to form a mixture; and

(b) tabletting said mixture.

Claim 14 (Currently amended) The process as defined in claim 13, wherein [the] said tabletting is conducted under direct compression.

Claim 15 (Original) The process as defined in claim 13 wherein said polymer and drug are blended by means of wet granulation followed by dry blending.

Claim 16 (Original) The process as defined in claim 13 wherein all material are wetted prior to said blending and dried and milled after said blending.

(Remainder of page left intentionally blank.)

Remarks

First, Applicant states that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made. As evidence of such, Applicant submits as Exhibit A, attached hereto, a copy of the Employees Confidentiality and Intellectual Property Agreement entered into by Mr. Saul Rios October 29, 1999 and by Jose Gutierrez-Rocca June 3, 1999 with the Kos Pharmaceuticals, Inc. ("Kos"), the assignee of the pending application.

Claims 1-5 and 7-16 are currently pending in the application. Applicant has amended claims 9, 11, 13, and 14 to advance the prosecution of the pending application. The amendments do not add new matter nor introduce new issue(s) and entry of these amendments is respectively requested.

Claims 2, 5, 7, 8, and 12 have been cancelled without prejudice.

The Examiner has rejected claims 1-5 and 7-16 under 35 U.S.C. 103(a) as being unpatentable over Chungi et al. (6,306,436). As the Examiner states, the test for obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 892, 18 U.S.P.Q. 2d 1885 (Fed. Cir. 1991). Applicant respectfully submits that the Examiner has not established a prima facie case of obviousness.

Chungi claims a composition containing the active ingredient Bupropion HCL. The composition includes a carrier present in an amount effective to provide a sustained release profile such that approximately 70 weight percent to 80 weight percent of the Bupropion HCL is released from the dosage form within a four-hour period and will generally make up 15 weight percent to 40 weight percent of the composition (Chuntgi: Col 6; 20-24). In Examples 1-4, the Bupropion formulations that utilize the Kollidon SR as a pharmaceutically acceptable carrier, do not utilize cellulose ether polymers s a pharmaceutically acceptable carrier.

In contrast, the pending application is directed to a formulation having a first component comprising a combination of 80 weight percent of polyvinyl acetate (PVA) and 20 weight percent of polyvinyl pyrrolidone (PVP), known as Kollidon SR (see Exhibit B attached hereto). Kollidon SR is a commercially available powder that consists of 8 parts PVA and 2 parts PVP designed as an excipient for imparting sustained release properties to a formulation. However, the inventors to the present invention surprisingly found that when the Kollidon SR is combined with cellulose ether polymers (CEP) and the combination is associated with a water soluble medicament to create a sustained release formulation, the Kollidon SR and CEP have a synergistic effect as regards the release of the medicament from the formulation. Thus, the present invention is directed to the association of Kollidon SR and CEP in a formulation to modulate the release of water soluble medicaments there from. In sum, Chungi taken as a whole, doesn't make the present invention obvious.

Applicant respectfully requests entrance of the present amendment and submits that the present application is in condition for allowance. Should the Examiner have questions or require additional information or clarification, please call the undersigned at the telephone number indicated below.

Respectfully submitted,

Karen J. Messick, Esq.
Registration Number 46,256
Attorney for Applicants

Kos Pharmaceuticals, Inc.
2200 North Commerce Parkway
Suite 300
Weston, FL 33326
Tel.: 954.331.3825
Fax: 954.331.3867

Date: 4/18/05

CERTIFICATION UNDER 37 C.F.R., §1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Mail Stop Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

4/18/05
Date

Jared Silberhorn

Kos Pharmaceuticals, Inc.

EMPLOYEE'S CONFIDENTIALITY AND INTELLECTUAL PROPERTY AGREEMENT

This Agreement made and entered into this 3rd day of June 1999, by and between Kos Pharmaceuticals, Inc., a Florida corporation, and its subsidiaries, successors, and assigns (hereinafter referred to for the purposes of this Agreement as "Kos" or "the Company") Jose C. Gutierrez-Rocca (hereinafter called "Employee") and the heirs, executors, administrators, and assigns of Employee.

In consideration of the employment or continued employment of Employee by Kos and of any salary, wages, bonuses, stock options, or other compensation to be paid or awarded by Kos to Employee, it is hereby agreed as follows:

As used in this Agreement, the following definitions apply:

"Confidential Information" means information disclosed -- whether orally or in writing -- to Employee, or otherwise known to Employee as a direct or indirect result of his or her employment by Kos, concerning (i) Kos' products, patent applications, research activities, formulations, processes, protocols, procedures, other intellectual properties, machines, services, and all matters having to do with the business or operations of the Company, including, but not limited to, all information of any type related to research, product development, manufacturing, quality matters, purchasing, finance, data processing, engineering, facilities, marketing, merchandising and selling, personnel, organizational matters, policy matters, legal and other corporate affairs and (ii) information of any type about any third party with which Kos is in technical or commercial cooperation, acquired by Employee, directly or indirectly, in connection with his or her employment by Kos. Included in the foregoing definition by way of illustration, but not limitation, are such items as research projects, findings or reports, business plans and projections, formulae, processes, methods of manufacture, computer programs, sales, costs, pricing data, regulatory matters, operating procedures, information about employees and personnel practices, and lists of investigators, consultants, suppliers and customers.

"Invention" means any discovery, invention, improvement, design, formula, analytical method, writing, computer system or process, manufacturing or other process, product, device, or other intellectual property, conceived, discovered or made by Employee during the term of employment, whether during or after working hours, and for 12 months after the term of employment, either solely or jointly with others, whether or not subject to patent or copyright laws, that is related to the actual or anticipated business or activities of Kos, or related to its actual or anticipated research projects, or suggested by or resulting from any tasks assigned to Employee or work performed by Employee for or on behalf of Kos, or with the use of Kos' equipment, facilities, materials or personnel, or in any other way related to the course or scope of Employee's employment by Kos or related to Confidential Information of Kos.

EXH. A

1. Disclosure of Confidential Information

Employee acknowledges that such Confidential Information is a valuable asset of Kos and that unauthorized disclosure or utilization thereof could be detrimental to Kos. Employee, therefore, shall not, either during or after the term of employment with Kos, disclose in any way or to any extent, to any person or organization other than Kos, or utilize for the benefit or profit of Employee or any other person or organization other than Kos, any Confidential Information, except (a) as may be authorized in writing in advance by Kos; (b) is publicly available or becomes publicly available other than through a breach of this Agreement by the Employee or, based on the Employee's knowledge, the breach of this Agreement by others; and (c) upon prior notification to Kos, Employee may be required by law to disclose.

2. Ownership of Intellectual Property

The following shall be the sole and exclusive property of Kos without further compensation to Employee:

(a) Any Inventions conceived, discovered or made by Employee;

(b) Any patent, patent application or record relating to any Invention.

3. Disclosure of Inventions

Employee shall promptly disclose to Kos and keep adequate records on any Invention of Employee.

4. Obtaining and Enforcement of Patents

Without further consideration from, or charge to Kos, whenever requested to do so by Kos, Employee shall execute any applications, assignments or other instruments that Kos shall consider necessary to apply for and obtain Letters Patent in the United States or any foreign country or otherwise to protect Kos' interest therein. These obligations shall continue beyond the termination of Employee's employment with Kos. Necessary expenses in connection with the foregoing, including a fee not to exceed $100 per day for testifying if Employee is no longer employed by Kos, shall be borne by Kos.

5. Disclaimer

Employee represents that Employee is under no obligation to any former employer or third party that is in any way inconsistent with this Agreement or that imposes any restrictions on Employee's activities with Kos, except as described in any attachment to this Agreement.

6. Confidential Information of Prior Employers

Employee shall not disclose to Kos or induce Kos to use any secret or confidential information or material belonging to others, including former employers, if any. In case of doubt with respect to Employee's obligations towards a prior employer, Employee shall consult with appropriate Company counsel.

7. Return of Kos Property

Upon termination of Employee's employment with Kos, or at such other times as requested by Kos, Employee shall turn over to a designated individual employed by Kos all written Confidential Information then in Employee's possession or custody. Employee shall not retain beyond his employment any originals, copies or other reproductions or correspondence, memoranda, reports, notebooks, drawings, photographs, or other documents relating in any way to the affairs of Kos without the prior written consent of Kos.

8. Miscellaneous Provisions

(a) Any failure on the part of Kos to insist upon the performance of this Agreement, or any part of thereof, shall not constitute a waiver of any right under this Agreement.

(b) In the event any provision, or any portion of any provision, of this Agreement should be declared invalid or unenforceable for any reason by a court of competent jurisdiction, such provision or portion thereof shall be considered separate and apart from the remainder of this Agreement, which shall remain in full force and effect.

(c) This agreement shall be construed according to the laws of the State of Florida.

IN WITNESS WHEREOF the parties have hereunto set their hands this 3rd day of June 1999.

06/15/99
Employee

For Kos

Kos Pharmaceuticals, Inc.

EMPLOYEE'S CONFIDENTIALITY AND INTELLECTUAL PROPERTY AGREEMENT

This Agreement made and entered into this 29h day of October, 1999, by and between Kos Pharmaceuticals, Inc., a Florida corporation, and its subsidiaries, successors, and assigns (hereinafter referred to for the purposes of this Agreement as "Kos" or "the Company") Saul A. Rios (hereinafter called "Employee") and the heirs, executors, administrators, and assigns of Employee.

In consideration of the employment or continued employment of Employee by Kos and of any salary, wages, bonuses, stock options, or other compensation to be paid or awarded by Kos to Employee, it is hereby agreed as follows:

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"Invention" means any discovery, invention, improvement, design, formula, analytical method, writing, computer system or process, manufacturing or other process, product, device, or other intellectual property, conceived, discovered or made by Employee during the term of employment, whether during or after working hours, and for 12 months after the term of employment, either solely or jointly with others, whether or not subject to patent or copyright laws, that is related to the actual or anticipated business or activities of Kos, or related to its actual or anticipated research projects, or suggested by or resulting from any tasks assigned to Employee or work performed by Employee for or on behalf of Kos, or with the use of Kos' equipment, facilities, materials or personnel, or in any other way related to the course or scope of Employee's employment by Kos or related to Confidential Information of Kos.

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8. Miscellaneous Provisions

(a) Any failure on the part of Kos to insist upon the performance of this Agreement, or any part of thereof, shall not constitute a waiver of any right under this Agreement.

(b) In the event any provision, or any portion of any provision, of this Agreement should be declared invalid or unenforceable for any reason by a court of competent jurisdiction, such provision or portion thereof shall be considered separate and apart from the remainder of this Agreement, which shall remain in full force and effect.

(c) This agreement shall be construed according to the laws of the State of Florida.

IN WITNESS WHEREOF the parties have hereunto set their hands this 29th day of October, 1999.

Employee

For Kos

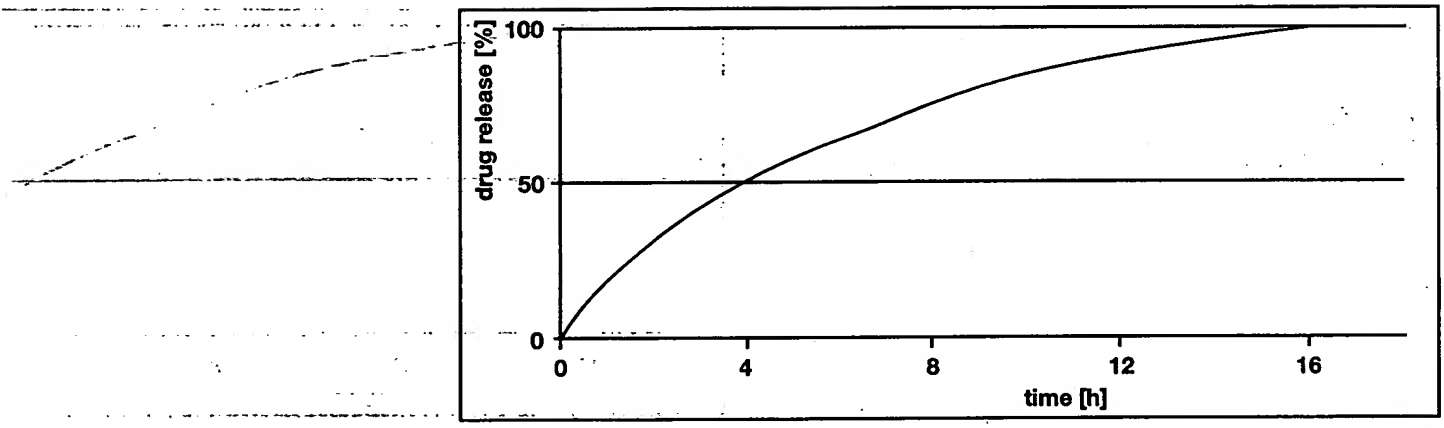
Technical Information

Kollidon® SR

January 2004
Supersedes Issue of July 2001

Register 2

Polyvinyl acetate and povidone based matrix sustained release excipient



Fine Chemicals

BASF

EXH. B

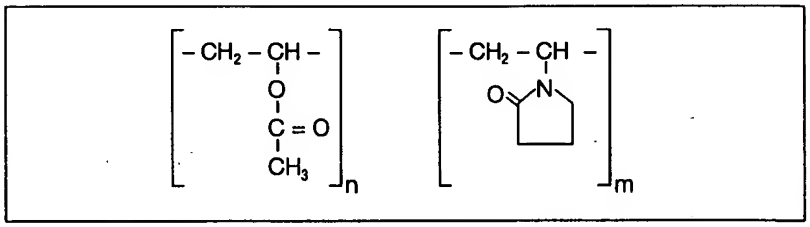
Contents

1. Introduction

1.1 General

Kollidon® SR is a polyvinyl acetate and povidone based matrix retarding agent. It is particularly suitable for the manufacture of pH-independent sustained-release matrix tablets. Polyvinyl acetate is a very plastic material that produces a coherent matrix even under low compression forces. When the tablets are introduced into gastric or intestinal fluid, the water soluble povidone is leached out to form pores through which the active ingredient slowly diffuses outwards. Kollidon® SR contains no ionic groups and is therefore inert to drug substances. The sustained-release properties are unaffected by ions or salts.

1.2 Chemical structure



1.3 Trivial name

Polyvinyl acetate / polyvinylpyrrolidone

2. Compositions

Kollidon® SR consists of 80% polyvinyl acetate and 19% povidone Ph.Eur./USP (Kollidon® 30) in a physical mixture.

Approx. 0.8% of sodium laury sulfate and about 0.2% of silica are used as stabilizers.

3. Specifications and methods

3.1 Specifications

Identification (IR spectra):	conforms
pH (10% in water):	3.5–5.5
Loss on drying (140°C, 60 min. vacuum):	< 5.0%
Sulphated ash:	< 2.0%
Heavy metals:	< 20 ppm
Vinyl acetate (HPLC):	< 100 ppm
Residual solvents, class III (acetic acid, formic acid)	< 0.5%
Microbiological status (10% in water):	conforms to Ph.Eur. categories 2 + 3A
Content of povidone	18.0–21.0%
Content of polyvinyl acetate	74.0–84.0%

Unless it is stated to the contrary the methods are taken from the current edition of the European Pharmacopoeia (Ph.Eur.).

3.2 IR-spectra

The IR-spectra is measured in potassium bromide and a typical spectra is given in the following figure 1.

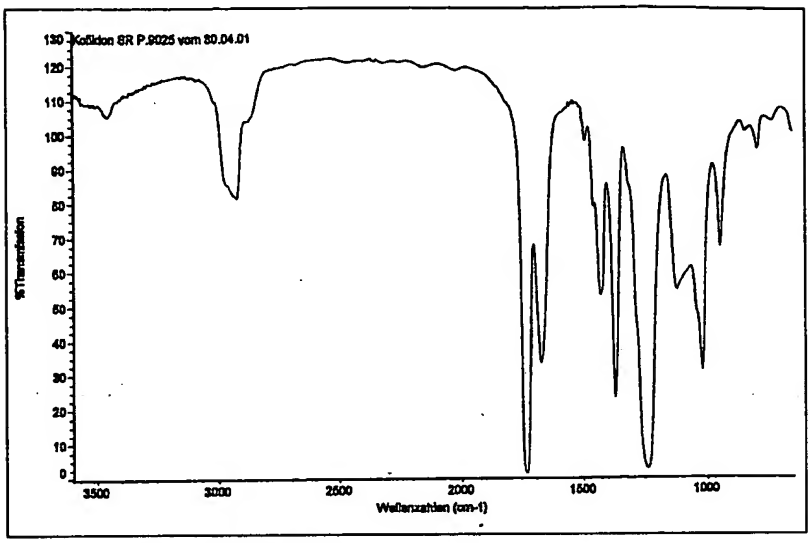


Fig. 1: IR-spectra of Kollidon® SR

3.3 Vinyl acetate

The monomer vinyl acetate is determined by the following HPLC method:

Principle:
The sample is dissolved and separated by liquid reversed phase chromatography. The interfering polymeric components of the matrix are removed by column switching. A UV detector operating at 205 nm and a calibration with an external standard are used to determine the level of vinyl acetate (detection limit 20 ppm).

Sample preparation:
Weigh approx. 150 mg of Kollidon SR accurate to 0.01 mg, into a 25-ml volumetric flask, dissolve in 10 ml of acetonitrile. Then make up the mark with the same solvent and shake for 30 minutes. Use aliquots of this solution for the HPLC analysis.

Preparation of the calibration solutions:
Weigh 40-50 mg of vinyl acetate, accurate to 0.01 mg, into a 50-ml volumetric flask and dissolve in about 20 ml of eluent. Then make up to the mark with eluent.
Prepare a series of dilutions from this stock solution to cover the expected range of vinyl acetate content in the sample of Kollidon SR.

Chromatographic conditions

Guard column:	25 x 4 mm cartridge packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Separation column:	250 x 4 mm steel column packed with LiChrospher® 60 RP select B, 5 µm (Merck)
Eluent (mobile phase):	Water/acetonitrile 92 + 8 (% w/w)
Flow rate:	About 1.2 ml/min
Sample volume	About 30 µl
Detection wavelength:	205 nm
Pressure	About 200 bar
Column temperature:	40°C
Retention time:	12 - 14 min

Column switching:
The analysis is started with the guard column and separation column in series. After about 1.2 minutes, the valves, controlled by the detector programme, switch over such that the eluent flows past the guard column, direct to the separation column. The columns are switched when the components to be determined, but not the interfering matrix, have already reached the separation column. Simultaneously, the guard column is washed out in the reverse direction by a second pump to remove the unwanted matrix components.
After about 18 minutes, the valves are reset to the starting position for the next analysis.
Figure 2 shows a typical chromatogramm obtained under these conditions.

Calibration factor:

$$F = \frac{A_{St}}{W_{St}}$$

A_{St} = calibration substance peak area [mV s]
W_{St} = weight of calibration substance per 100 ml [mg/100 ml]

Calculation of vinyl acetate in the sample:
The content of the sample is calculated with the aid of an external standard:

$$\text{vinyl acetate (ppm)} = \frac{A}{F \cdot W_{Sa}} 10^6$$

A = peak area of vinyl acetate in the sample [mV s]
W_{Sa} = sample weight [mg/100 ml]

Linearity:
The calibration curves were plotted from 5 points covering a concentration range of 0 -1.0 µg/ml to check their linearity. A linear calibration curve was obtained.

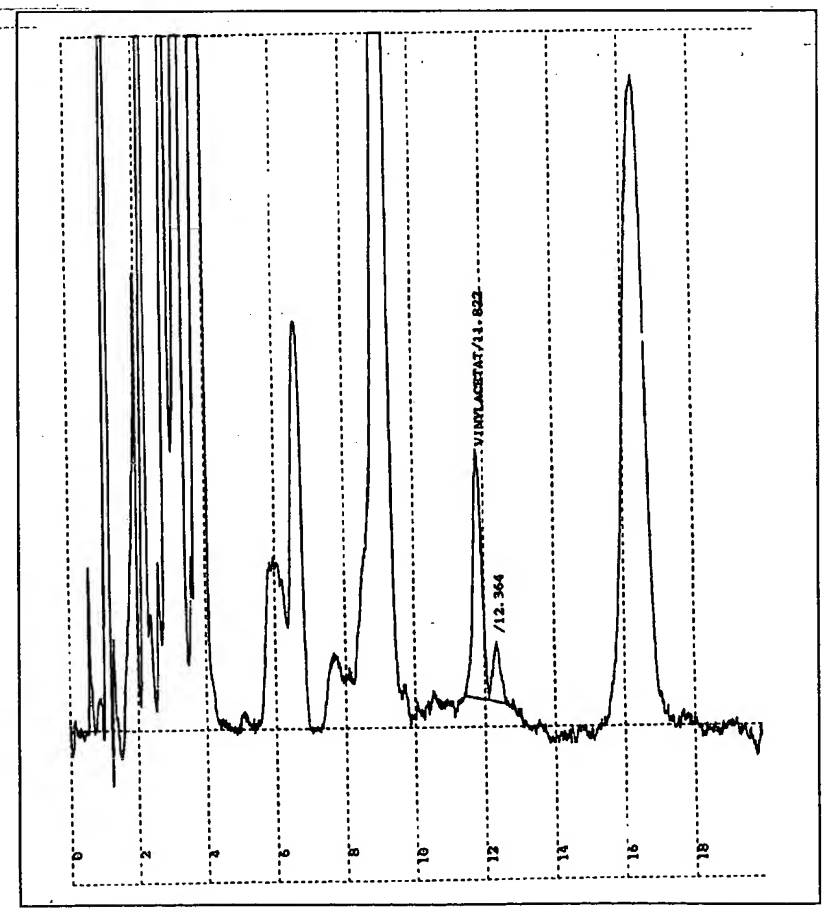


Fig. 2: Typical chromatogram

3.4 Content of povidone

Determine the nitrogen content in 1.0 g of Kollidon® SR according to the Ph.Eur. monograph "Povidone" and calculate the content of povidone as follows:

$$\text{Povidone in Kollidon® SR (\%)} = \frac{\text{Nitrogen content (\%)}}{0.126}$$

3.5 Content of polyvinyl acetate

Determine the saponification value (Ph.Eur. 2.5.6) in 1.5 g of Kollidon® SR and calculate the content of polyvinyl acetate as follows:

Polyvinyl acetate in Kollidon® SR (%) = Saponification value x 0.1534

4. Properties

Description

White or slightly yellowish, free-flowing powder.

Solubility

Insoluble in water (The povidone part is soluble but the polyvinyl acetate part is not soluble).
It is very soluble in N-methylpyrrolidone.

Molecular weight, K-value

The average molecular weights Mw of the polyvinyl acetate part is about 450,000 and of the povidone K 30 part it is about 50,000.

The average molecular weight of Kollidon® SR as mixture is expressed as K-value according to the method described in the monographs "Povidone" and measured in a 1% solution in tetrahydrofurane.
The typical K-value is 60 to 65.

Particle size distribution

The average particle size is about 100 µm.

Glas transition temperature

The glas transiition temperature Tg of the anhydrous material is about 35°C.

Bulk density

About 0.45 g/ml.

Flowability

Kollidon® SR has outstanding flow properties with a repose angle well below 30°. It can enhance the flowability of other components added for a tablet formulation.

Hygroscopicity

The water uptake is much less than that of povidone or copovidone. Figure 3 shows the water sorption and desorption isotherms at room temperature.

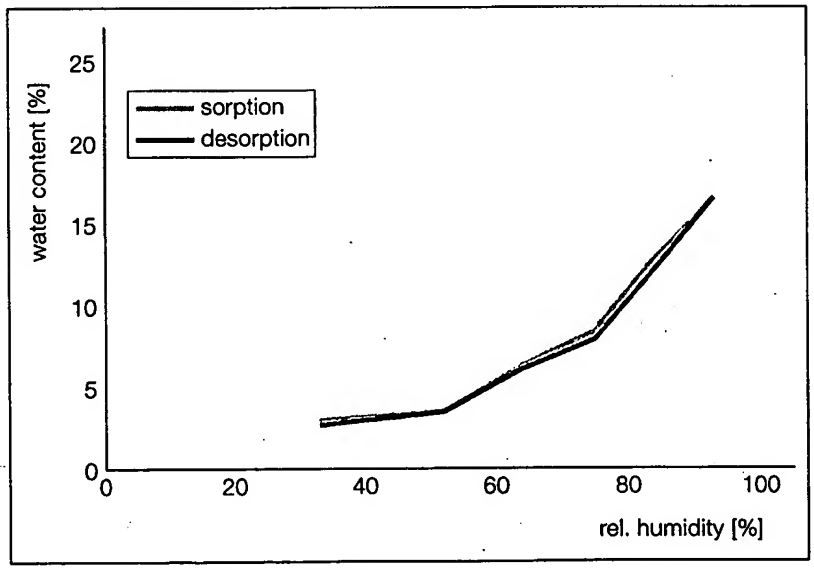


Fig. 3: Sorption isotherms of Kollidon® SR

Compressibility

Kollidon® SR has excellent compressibility and endows tablets with enormous hardness and low friability. This is due to the combination of the very plastic polyvinyl acetate and the also strongly binding povidone.

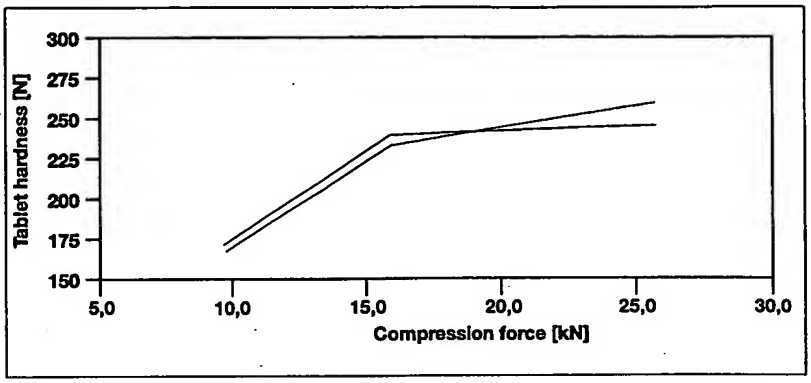


Fig. 4: Hardness-compression force profile of propranolol sustained release tablets containing 50% of Kollidon® SR (2 Lots, Formulation see chapter 6.2)

5. Registration

5.1 Pharmacopoeia

No pharmacopoeial monograph is available for Kollidon® SR as a physical mixture of two polymers.
Kollidon® 30 used for the production of Kollidon® SR meets the requirements of the Povidone monograph in Ph.Eur., USP and JP.

5.2 Drug Master File

For registration purposes a US-DMF was filed (No.15 460).

5.3 Analytical monograph

For registration purposes a Pharmacopoeia like monograph of Kollidon® SR was prepared including all analytical methods and limits. It is available on request.

5.4 Description of synthesis

For registration purposes a short description of the production of Kollidon® SR is available on request.

5.5 Use of polyvinyl acetate in drugs and food

Polyvinyl acetate is used in a variety of drugs for oral administration in numerous countries including Germany, France, Japan and USA.
Polyvinyl acetate also is allowed in the food industry in several countries like Germany, USA and Japan.

6. Applications

6.1 General Informations

Kollidon® SR can be used for the production of the following sustained release matrix dosage forms: Tablets, pellets and granules.

Different technologies to obtain such dosage forms can be applied:
Direct compression, roller compaction, wet granulation and extrusion.

The excellent flowability and compressibility of Kollidon® SR makes this excepient particulary suitable for the manufacture of sustained release tablets obtained by **direct compression**.

The required content of Kollidon® SR in the tablet depends on the solubility of the active ingredient. The following table gives an information about the usual amounts of Kollidon® SR to obtain a sustained release during 12-24 hours.

Solubility of the active ingredient	**Kollidon® SR in the tablet**
Very slightly soluble to practically insoluble	15 - 25%
Sparingly soluble to slightly soluble	25 - 40%
Soluble to freely soluble	40 - 55%

The sustained release characteristics can be modified by varying the Kollidon® SR content in the formulation. Figure 5 shows the influence of the amount of Kollidon® SR on the release of caffeine as a example of a soluble active ingredient.

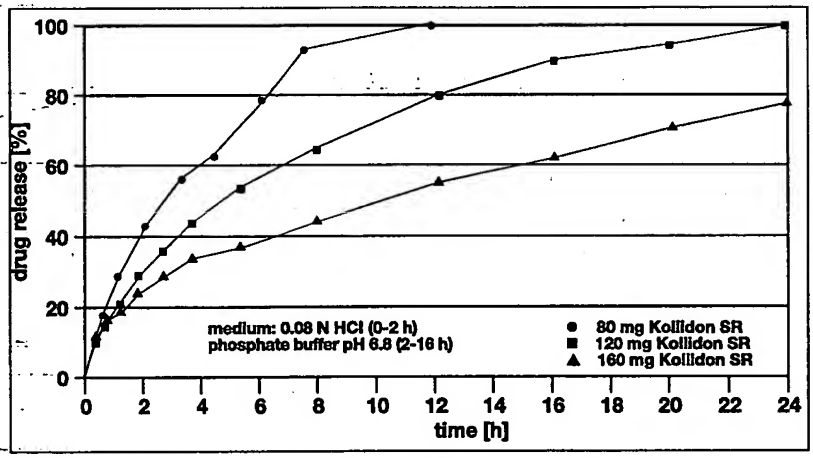


Fig. 5: Influence of the amount of Kollidon® SR on the drug release in a caffeine sustained release tablet (160 mg Caffeine)

In the case of slightly soluble or practically insoluble drug substances the release can be accelerated not only by reducing the content of Kollidon® SR but also by the addition of hydrophilic substances like lactose, Kollidon® 30 or Kollidon® CL-M which act as pore former.

Interesting and important properties of sustained release matrix tablets based on Kollidon® SR are the following:
1. The drug release is independent of the pH (see figure 6).
2. The drug release is independent of the ionic strength of the dissolution medium (see figure 6, addition of 2.5% of NaCl).
3. The drug release is independent of the usual compression force and tablet hardness (see figure 7).

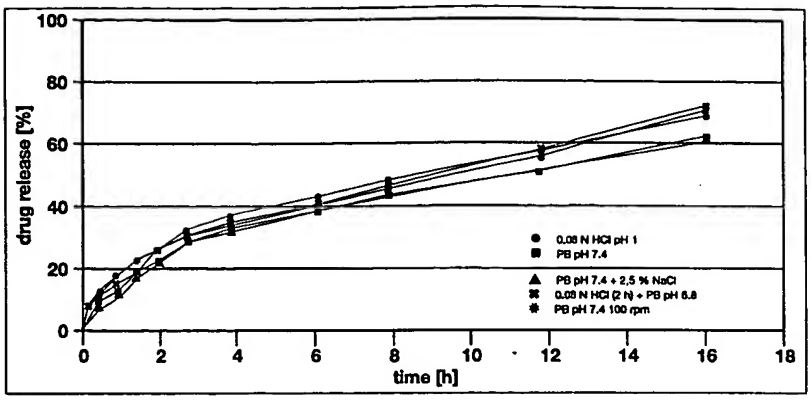


Fig. 6: Influence of the pH and the ionic strength of the dissolution medium on the release of caffeine tablets (Caffeine + Kollidon® SR 1+1)

It is recommended to store the matrix tablets containing Kollidon® SR at temperatures below 30°C and in tightly closed containers to avoid the uptake of humidity which could modify the release profile of formulations containing a higher percentage of Kollidon® SR.

In the following chapters three typical examples of soluble and practically insoluble active ingredients are given in form of sustained release tablets. Further formulations can be found in the "Generic Drug Formulations" 3rd edition (BASF, CD-ROM 2003, MER 0010).

6.2 Propranolol Sustained Release Matrix Tablets

Formulation

	Parts by weight [g]	Composition [%]
Propranolol-HCl	160.0	49.23
Kollidon® SR	160.0	49.23
Silicon dioxide, colloidal	3.4	1.05
Magnesium stearate	1.6	0.49
Total	325.0	100.00

Manufacture

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a Turbula mixer and then pressed on a rotary press.

Tablet properties

Diameter	10 mm
Weight	330 mg
Compression force	10 kN / 18 kN / 25 kN
Hardness	170 N / 235 N / 250 N
Friability	0.1%
Drug release	See Figure 7

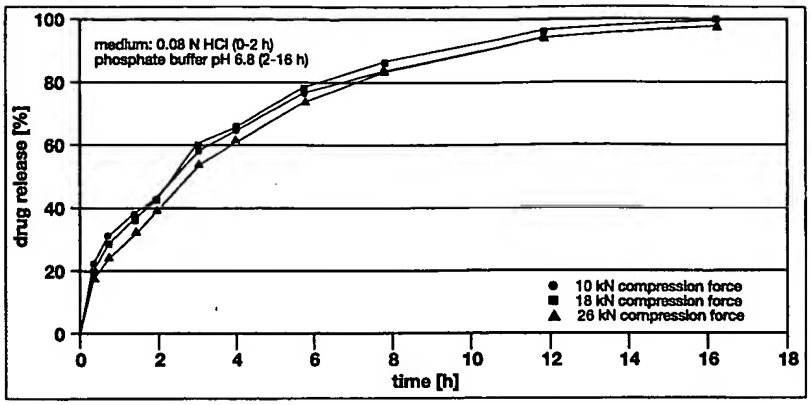


Fig. 7: Propranolol sustained release tablets: Influence of the compression force on the drug release

6.3 Diclofenac Sustained Release Matrix Tablets

Formulation

	Weight	Percent
Diclofenac sodium	100 g	48.4
Kollidon® SR	100 g	48.4
Aerosil 200	3.4 g	1.6
Magnesium stearate	3.4 g	1.6

Manufacture: All ingredients are mixed, passed through a 0.8 mm sieve and pressed with a medium compression force on a rotary press.

Tablet properties

Diameter	8 mm
Weight	206 mg
Compression force	medium
Hardnes	195 N
Friability	<0.1%
Drug release	See Figure 8

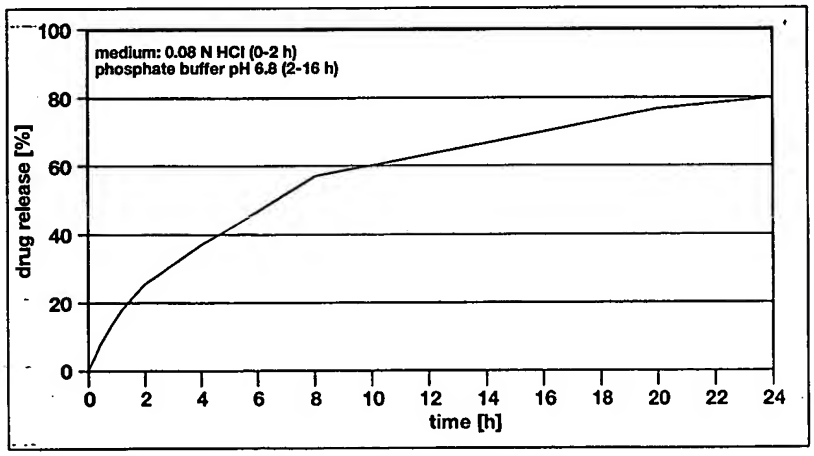


Fig. 8: Dissolution of Diclofenac sustained release tablets

6.4 Theophylline Sustained Release Matrix Tablets

Formulation

	Parts by weight [g]	Composition [%]
Theophylline gran.	500.0	53.9
Kollidon® SR	200.0	21.6
Ludipress® LCE	225.0	24.2
Magnesium stearate	3.0	0.3
Total	928.0	100.00

Manufacture

All ingredients were passed through a 0.8 mm sieve, blended for 10 min in a Turbula mixer and then pressed on a rotary press.

Tablet properties

Diameter	19.0 x 8.5 mm (football shape)
Weight	928 mg
Compression force	11 kN
Hardness	172 N
Friability	<0.1%
Drug release	See Figure 9

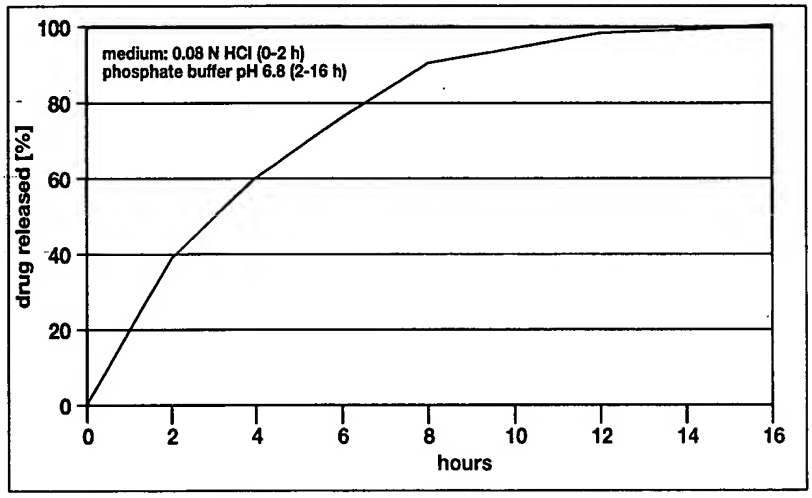


Fig. 9: Dissolution of theophylline sustained release tablets

7. Storage

Store below 30°C

8. Stability

At least 24 months in the unopened original container at room temperature.

9. PBG-Number

10235112

10. Packaging

20 kg plastic container

Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	10/086,059
Filing Date	02/27/2002
First Named Inventor	Rocca
Art Unit	1617
Examiner Name	Theodore J. Criares
Attorney Docket Number	200541-7095

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Rely Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 50-2543

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☑ Other any additional fees as necssary

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	Karen J. Messick, Esq.	*Registration No. (Attorney/Agent)*	46,256
Signature		*Date*	4/18/05

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Name (Print/Type)	Jared G. Silberhorn		
Signature		Date	4/18/05

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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